

Breast Cancer Screening and Diagnosis

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Mammograms

- **Screening Mammography**
 - **Asymptomatic women**
 - **≥ 35 years**
- **Diagnostic Mammography**
 - **Breast Related Complaints**
 - **Palpable abnormalities, pain, suspicious nipple discharge**
 - **Personal history of breast cancer**
 - **Patients under screening age**
 - **Male patients**

Regulation of Mammography

- **1985 Survey of US mammography facilities by FDA**
 - 36% of facilities producing images of unacceptable quality
 - 15% of facilities utilizing general purpose x-ray equipment for mammography
- **1990 GAO survey**
 - Many mammography facilities lacked adequate quality assurance programs
- **1992 Senate Committee on Labor and Human Resources**
 - Hearings on quality issues in mammography

Regulation of Mammography

- **Mammography Quality Standards Act of 1992**
 - Annual inspections
 - Equipment
 - Image quality and quality assurance
 - Standards for interpreting physicians, technologists, physicists
 - Patient notification of results and image retention

BI-RADS

- **Breast Imaging Reporting and Data System**

- **Standardize reporting and facilitate outcomes monitoring**
- **Assessment Categories**

BI-RADS 0	Assessment Incomplete
BI-RADS 1	Negative
BI-RADS 2	Benign Findings
BI-RADS 3	Probably Benign Findings
BI-RADS 4	Suspicious Abnormality
BI-RADS 5	Highly Suggestive of Malignancy
BI-RADS 6	Known Malignancy

Breast Cancer in the United States

- **Most common cancer in women:**
 - 1:8 by age 95
 - 20% in women <50 years of age
- **Breast cancer incidence increasing**
 - 1% per year
- **Breast cancer death rate decreasing**
 - 30% decrease since 1988

Female Cancer Estimates 2012 USA

	New Cases	Deaths
Breast	232,340-Invasive 63,300-In-Situ	39,620
Colon	52,390	24,530
Cervical	12,340	4,030
Lung	110,110	72,220
Pancreas	22,480	18,980

Siegel CA: A Cancer Journal 2013

Screening Mammography

- **Areas of Agreement**
 - **Screening mammography saves lives for women aged 39-69 based upon meta analysis of randomized controlled studies**
 - **Screening recommended for normal risk women aged 50-74**
 - **Screening mammography is an imperfect test**
 - **Limitations/Harms exist**
 - **Maximum benefit of 65% mortality reduction**
 - **Informed patient decision**

Screening Mammography

- **Effective**
 - Scientific proof of benefit in decreasing breast cancer mortality
 - Death rate in US from breast cancer unchanged for 50 years prior to 1990
 - Mammographic screening begins in mid-1980's
 - Increase in cancer incidence
 - 1990 decrease in death rate from breast cancer
- **Available and Reproducible**
 - Over 12,000 mammography units in U.S.
- **Affordable**
 - Still around \$100 in most of U.S.

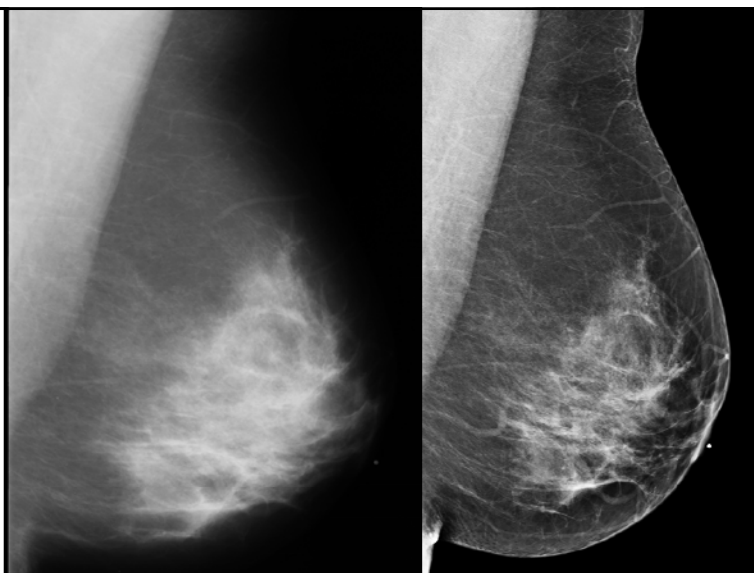
Screening Mammography Proof of Benefit

- **Direct Proof of Benefit**
- **Randomized Controlled Trials**
 - Compare mortality of study group with control group
 - RCTs underestimate mortality benefit

Screening Mammography

Proof of Benefit

- Indirect Proof of Benefit
 - Measure Surrogate End Points
 - Tumor size
 - Axillary lymph node involvement
 - Stage at diagnosis
 - Stage 0 or 1 breast cancer
 - Less morbidity from cancer treatment
 - Less extensive surgery
 - Less frequent radiation therapy
 - Less frequent chemotherapy
 - Less aggressive chemotherapy



Digital Mammography not included in RCTs or Modeling Data
DMIST Trial: 25-53% Improved Cancer Detection for Digital Mammography

- Dense Breasts
- Patients <50 years

The Evidence for Screening

- **HIP Trial (1963-1969)**
 - 62,000 women age 40-64 on entry
 - 31,000 women
 - Study group offered mammography and breast physical exam annually for 4 years
 - Attendance of study group first four screens
 - 67%, 54%, 50%, 46%
 - Demonstrated 30% statistically significant decrease in mortality

The Evidence for Screening

- **The Swedish Trials (1976-1988)**
 - 5 randomized controlled trials
 - All 5 trials showed overall benefit
 - 2-county trial published in 1985
 - » 31% statistically significant overall mortality reduction
- **Gothenburg RCT and Malmo RCT (1997)**
 - Showed statistically significant mortality reductions of 44% and 36% for women aged 40-49

The Evidence for Screening

- **Review of screening outcomes in nine counties in Sweden**
 - January 2006
 - 45% of the Swedish population
 - Death rate in screened group decreased 44% since 1977
 - **Results duplicated worldwide in organized screening programs**
 - British Columbia
 - Holland
 - Australia
 - Norway
 - Nova Scotia

Screening Guidelines

- **ACS 1997**
 - Annual mammography beginning at age 40
- **USPSTF 2002**
 - Screening mammograms every 1-2 years beginning at age 40
- **ACS 2003**
 - Average risk women begin annual mammography at 40
 - Older women continue annual screening as long as in good health and candidate for treatment
 - Women at increased risk may benefit from additional screening strategies (Earlier initiation, MRI, US)
- **ACS 2007**
 - Annual supplemental screening breast MRI women with $\geq 20\%$ lifetime risk of breast cancer

USPSTF 2009

- **No mammography recommended for:**
 - **Women ages 40-49**
 - **Discussion with physician if high risk**
 - **Women over age 74**
- **Mammography recommended every two years for:**
 - **Women ages 50-74**
- **No breast self examination**
- **No clinical breast examination**

USPSTF

- **17 experts on health care appointed by Agency of Health Care Quality and Research under Dept. of HHS**
 - **None with any expertise in diagnosing or treating breast cancer**
 - **Reviewed essentially the same data as in their review from 2002**
 - **Did not consider updated information of RCTs and screening data that was even more supportive of beginning screening at age 40**

USPSTF 2009

- **Evidence considered:**
 - **Randomized controlled trial data on screening mammography**
 - **CNBSS-1**
 - **AGE Trial**
 - **Harms of screening mammography**
 - **Age-specific screening results of BCSC**
 - **Modeling data from 20 different screening mammography regimens**

USPSTF 2009

- **Evidence not considered:**
 - **All peer reviewed studies assessing the benefit of screening mammography which were not RCTs**
 - **All service screening studies**
 - **All studies describing improvement in screening mammography since RCTs performed**
 - **All peer reviewed cost-benefit analyses of screening mammography**

USPSTF

- **Rationale for not screening women ages 40-49**
 - Claim only a 15% mortality reduction
 - Claim 1904 women must be invited to screen to prevent one death
 - Harms of screening exceed the benefits of screening
 - False positives, anxiety, distress, radiation exposure, overdiagnosis of DCIS

Screening Women Aged 40-49

- **No scientific basis for threshold of 50**
 - No abrupt change in screening parameters at age 50
- **Lowest possible mortality benefit used**
 - RCTs and screening data show 30-48% mortality reduction
- **Computer models favored over direct data**

Screening Women Aged 40-49

- **Breast Cancer is significant for women in their 40's**
 - 40% of all years lost to breast cancer are in women aged 40-49
- **Harms of not screening**
- **No data to support only screening high-risk women**
 - 80% of women diagnosed with breast cancers have no significant risk factors

Harms of Mammography Screening

- **False-positives(recall, biopsy)**
 - 5-15%
- **Pain(breast compression)**
 - 1-4%
- **False-negatives**
 - <1%
- **Radiation oncogenesis**
 - <<1%
- **Overdiagnosis**
- **Anxiety**

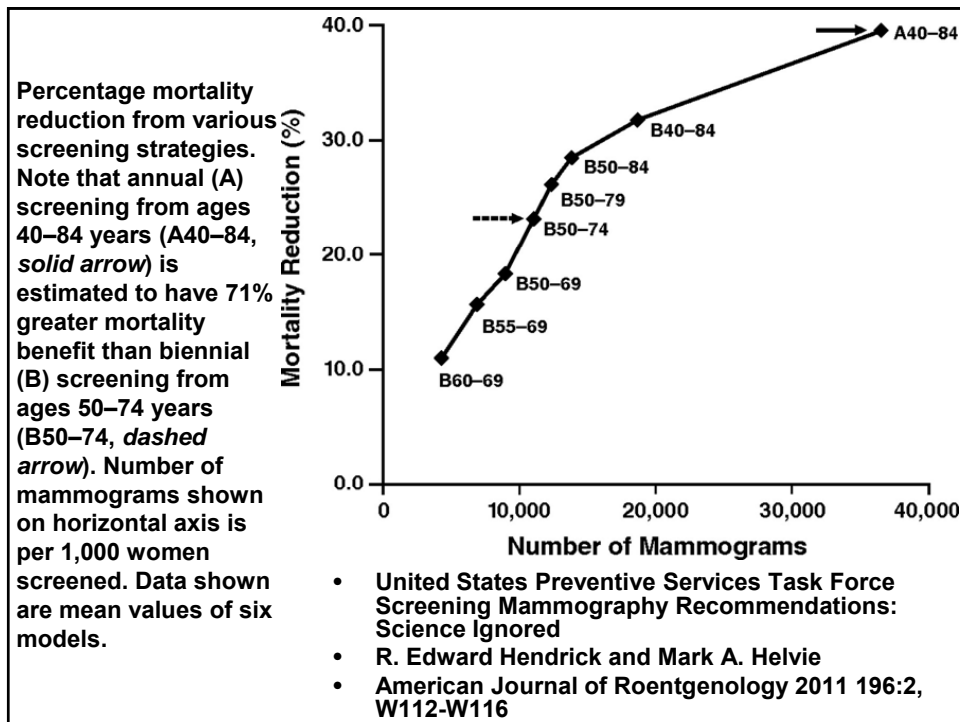
Harms of Mammography Screening

- **Average years of annual screening for one occurrence (Age 40-79)**
 - **False positive biopsy**
 - **149-233 years**
 - **4.3-6.7 per 1000 screened**
 - **Additional imaging**
 - **12-16 years**
 - **64-84 per 1000 screened**

Hendrick and Helvie, AJR 2011

USPSTF

- **Rationale for screening women aged 50-74 every two years**
 - **State that a large portion of the benefit of annual screening is maintained in biannual screening**
 - **Lose 15% of mortality benefit**
 - **State the harms are doubled by screening annually instead of biannually**



USPSTF

- **Rationale for no screening of women aged 75 and older**
 - Claim there are no studies that show a statistically significant mortality reduction in this group
 - An otherwise healthy woman at age 75 may now live much longer
 - Decision to screen should be based on co-morbidity, not age alone
 - Most women in this group have fatty breasts
 - Cancers are the easiest to find at an early stage

USPSTF Fallout

- **1 week later discovered at least 5 places in the original form of the U.S. Healthcare Reform Act that the government must accept and place into law USPSTF recommendations**
 - **A or B recommendations**
 - **Impact on coverage**

USPSTF Fallout

- **December 2009**
 - **Senate votes to amend health care bill to ensure routine mammogram insurance coverage to all women over 40**
 - **House votes 426-0 for resolution stating USPSTF guidelines not be used by insurers to deny screening mammogram coverage**
- **New HHS Screening Guidelines**
 - **New private health plans must cover evidence-based preventive services**
 - **Includes all services rated A or B by USPSTF**
 - **HHS specifically used USPSTF 2002 guidelines**
 - **2009 guidelines labeled by HHS as “Not considered to be current”**

Current Screening Guidelines

- **Age 40 and older**
 - **Annual mammograms**
 - **ACS, NCCN, ACOG, ACR**
 - **Every 1-2 years**
 - **NCI, HHS, FDA, AMA**
- **Age 50-74**
 - **Every 2 years**
 - **USTSTF(2009), ACP**

Evidence for Screening

- **September 2010**
 - **SCRY study evaluated mortality rates in 40-49 age group in patients who underwent screening versus those not screened**
 - **Evaluated 600,000 women with average follow-up of 16 years**
 - **Statistically significant decrease in breast cancer mortality of those screened 29%**

New data 2013

- **“A Failure Analysis of Invasive Breast Cancer” Webb, et al. September 2013 Cancer**
 - **Invasive breast cancers diagnosed 1990-1997 followed through 2007**
 - **609 confirmed breast cancer deaths**
 - **Median age at diagnosis 49**
 - **29% among women screened**
 - » **19% detected on first screen**
 - » **10% interval cancers**
 - **71% among unscreened women**
 - » **6% > 2 years**
 - » **65% never screened**

Current Screening Guidelines

- **Average risk general population**
 - **Age 40**
- **BRCA gene mutation**
 - **Age 25-30 for carriers or untested relatives**
- **First degree relatives of women with premenopausal breast cancer or women with $\geq 20\%$ lifetime risk based on family history**
 - **Age 25-30 or 10 years earlier than age of affected relatives**
- **Mantle radiation between ages 10 and 30**
 - **8 years after radiation therapy but not before age 25**
- **Biopsy proven lobular neoplasia, atypical ductal hyperplasia, DCIS, or invasive carcinoma**
 - **Any age after diagnosis**

High Risk Patients

- ACS recommends annual supplemental breast MRI examination for patients with $\geq 20\%$ lifetime risk of developing breast cancer
 - BRCA1/2 gene mutations
 - Untested first-degree relatives on carriers
 - Prior thoracic radiation therapy between ages 10 and 30
 - Genetic syndromes
 - Li-Fraumeni Syndrome
 - Cowden Syndrome
 - Bannayan-Ruvalcaba-Riley Syndrome

High Risk Patients

- Other factors
 - Family history
 - Prior biopsies showing hyperplasia, atypia, LCIS
 - Prolonged estrogen exposures

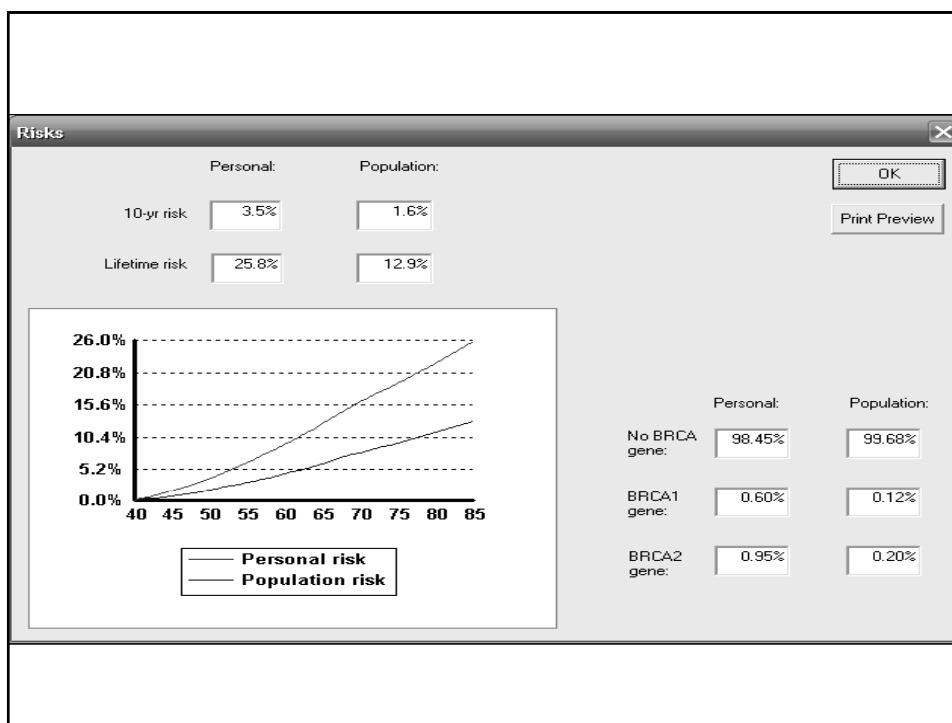
High Risk Patients

- **Models for determining risk**
 - **Gail Model**
 - **Claus Model**
 - **BRCAPRO**
 - **BOADICEA**
 - **Tyrer-Cuzick(IBIS)**
 - <http://www.ems-trials.org/riskevaluator/>

The screenshot displays the IBIS1 - IBIS Risk Evaluator software interface. The window title is "IBIS1 - IBIS Risk Evaluator". The interface is divided into several sections for data entry:

- Personal factors:** Includes fields for Woman's age (40), Menarche (12), Height (5 ft 2 in), Weight (10 stone 10 lb), and Measurements (Metric: Imperial).
- Reproductive history:** Includes checkboxes for Nulliparous, Parous, and Unknown, and a field for Age First Child (24). It also has checkboxes for No benign disease, Hyperplasia (not atypical), Unknown benign disease, Atypical hyperplasia, and LCIS.
- Menopausal status:** Includes checkboxes for Premenopausal, Perimenopausal, Postmenopausal, and No information, along with a field for Age at menopause.
- Family history:** Includes sections for Mother, Sisters, Paternal Grand, Maternal Grand, Paternal aunts, Maternal aunts, and Daughters. Each section has checkboxes for Ovarian, Bilateral, and Breast cancer, and a field for Age.
- Other factors:** Includes checkboxes for Ashkenazi inheritance, Male relatives, Half Sisters, Affected cousins, Affected Nieces, and Genetic Testing.
- HRT use:** Includes a checkbox for HRT use and a field for Length of use (years).
- Competing mortality:** Includes a checkbox for Competing mortality.
- Calculate Risk:** A button to calculate the risk.
- Family History Diagram:** A pedigree chart showing the family structure and affected individuals.

The status bar at the bottom indicates "Ready" and "FALSI".



Supplemental Screening

Sign Up to receive more info/Contact Us En Español

"Exposing the Secret" Jewelry Designs by Susan A. Katz for Are You Dense, Inc.

Are You DENSE?
exposing the best-kept secret®

Are You DENSE? Music Fest 2009
Are You DENSE? 2009
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Early Matters
stage of tumor at discovery influences prognosis
Be informed about your breast density •

Are You DENSE? FACT #1
Breast density is one of the strongest predictors of the failure of mammography screening to detect cancer.

WHAT IS dense breast tissue?
Dense breast tissue is comprised of less fat and more connective tissue which appears white on a mammogram. Cancer also appears white on a mammogram thus tumors are often hidden behind the dense tissue. As a woman ages, her breasts usually become more fatty.

HOW DO I KNOW if I have dense breast tissue?

WHAT DO I DO if I have dense breast tissue?
Talk to your doctor about having an ultrasound or breast MRI. Connecticut General Statute Sections 38a-503 and 38a-530 requires insurance companies to provide coverage for comprehensive ultrasound screening of an entire breast or breasts if a mammogram demonstrates heterogeneous or dense breast tissue based on the BIRADS (Breast Imaging Reporting and Data System) established by the American College of Radiology (ACR).

What's New
VIDEO: DR. CAPPELLO & DENSE SURVIVOR JAN DISCUSS IMPACT OF ARE YOU DENSE INC. IN PREVENTING DELAYED DIAGNOSES •
INVASIVE CANCER DETECTED AFTER NYTIMES ARTICLE ON ARE YOU DENSE

Supplemental Screening

- **Breast Density Reporting Laws**
 - **Require facilities to report breast density in patient post-exam letter**
 - **Heterogeneously dense and extremely dense based on BI-RADS**
 - **40% population**
 - **Some mandates include recommendation to discuss supplemental screening (US or MRI) with physician**
 - **Connecticut, Texas, Virginia, California, New York, Hawaii, Maryland, Tennessee, Nevada, Alabama, Oregon, North Carolina**

ACRIN 6666 Trial

- **2,809 women (2004-2007)**
 - **At least heterogeneously dense breast tissue**
 - **Elevated risk for breast cancer**
 - **Personal or family history of breast cancer**
 - **Prior breast biopsy demonstrating atypia**
 - **BRCA 1/2 gene mutations**
 - **Prior chest radiation between ages 10 and 30**
 - **Evaluated screening whole breast ultrasound in conjunction with mammography**
 - **Additional supplemental MRI component**

ACRIN 6666 Trial

Modality	Cancer detection rate
Mammography	7.6 cancers per 1000 women
Mammography and US	11.8 cancers per 1000 women
Mammography and MRI	14.7 cancers per 1000 women

No additional benefit in combining mammography, US, and MRI Cancers found were mostly <1cm and node negative

ACRIN 6666 Trial

- **Screening Whole Breast Ultrasound**
 - **BI-RADS 3**
 - **19.5%**
 - **PPV of biopsy recommendation**
 - **Mammography alone**
 - **29%**
 - **Mammography and screening ultrasound**
 - **11%**
 - **Increased sensitivity with decreased specificity compared to mammography alone**

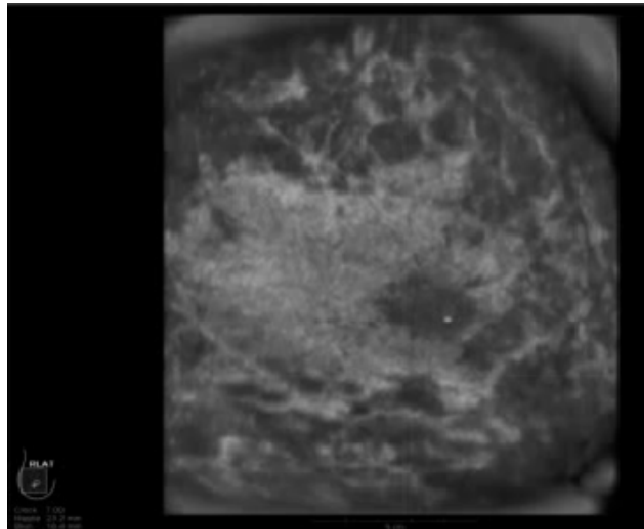
Automated Whole Breast Ultrasound

- **Alternative to manual handheld screening**
 - **First system FDA approved in 2012 as adjunct to mammography**
 - **Efficiently and quick scanning of both breasts**
 - **Reproducible technique**
 - **Drawbacks**

Automated Whole Breast Ultrasound



Automated Whole Breast Ultrasound



Digital Breast Tomosynthesis

- **FDA approved for diagnostic and screening mammography February 2011**
 - **Three-dimensional derivative of digital mammography**
 - **A series of individual low-dose images are obtained with the x-ray tube rotating over a limited arc above the compressed breast**
 - **Data reconstructed using mathematical algorithms into a series of thin-sliced images**
 - **High resolution 1mm thick slices**

Digital Breast Tomosynthesis

- **Anticipated benefits of DBT**
 - **Eliminates/reduces tissue superimposition**
 - **Screening recall reduction**
 - **Increased accuracy and PPV of mammography**
 - **Increased cancer detection**
 - **Increased visualization and characterization of masses and mass margins**
 - **Increased visualization of architectural distortion**

Digital Breast Tomosynthesis

- **Yale Study 2012**
- **Compared screening recall rates**
 - **Standard 2D FFDM versus Standard 2D FFDM and DBT**
 - **1800 patients**
 - **Recall rate 2D FFDM versus 2D FFDM and DBT**
 - **11.9% versus 4.9%**
 - » **59% recall reduction**

Digital Breast Tomosynthesis

Oslo Prospective Screening Trial

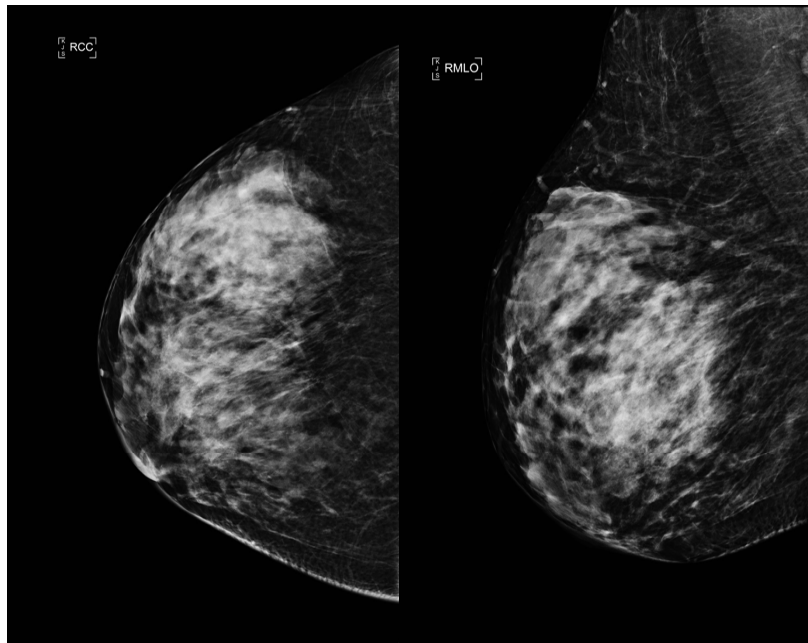
- 2 year long screening cycle
- Women 50-69 invited to have FFDM+DBT
- 12,631 examinations
- 4 modes independently read
 - FFDM, FFDM+CAD, FFDM+DBT, Synthetic FFDM+DBT
- 47% increase in detection of invasive cancers
- 27% increase in all cancers
- 15% decrease in false positives

Digital Breast Tomosynthesis

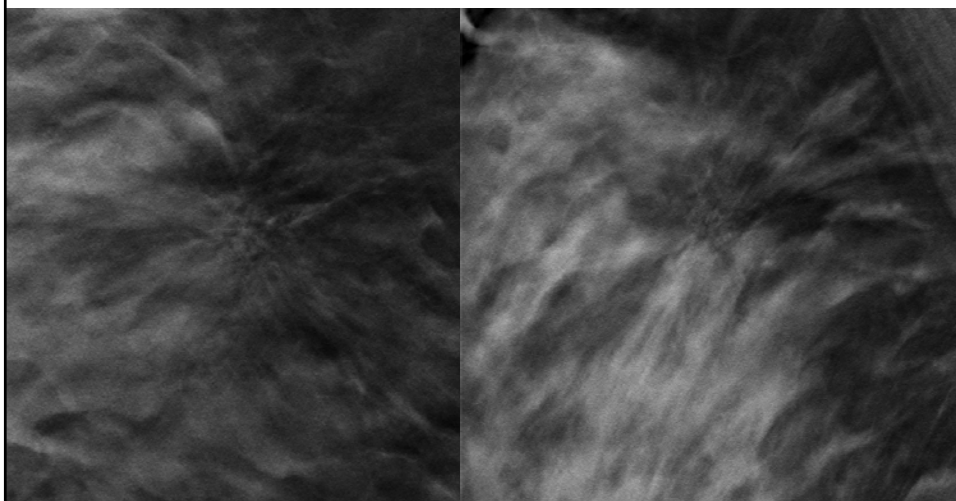
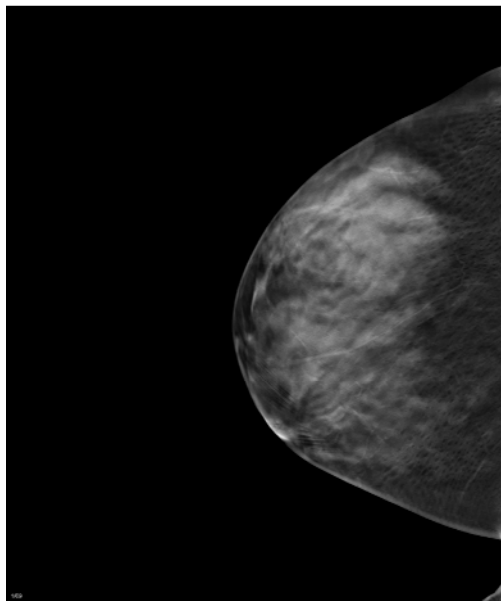
- **Issues to resolve**
 - Population for use
 - Larger patients or patients with implants
 - Interpretation time
 - Radiation Dose
 - Technology cost and reimbursement

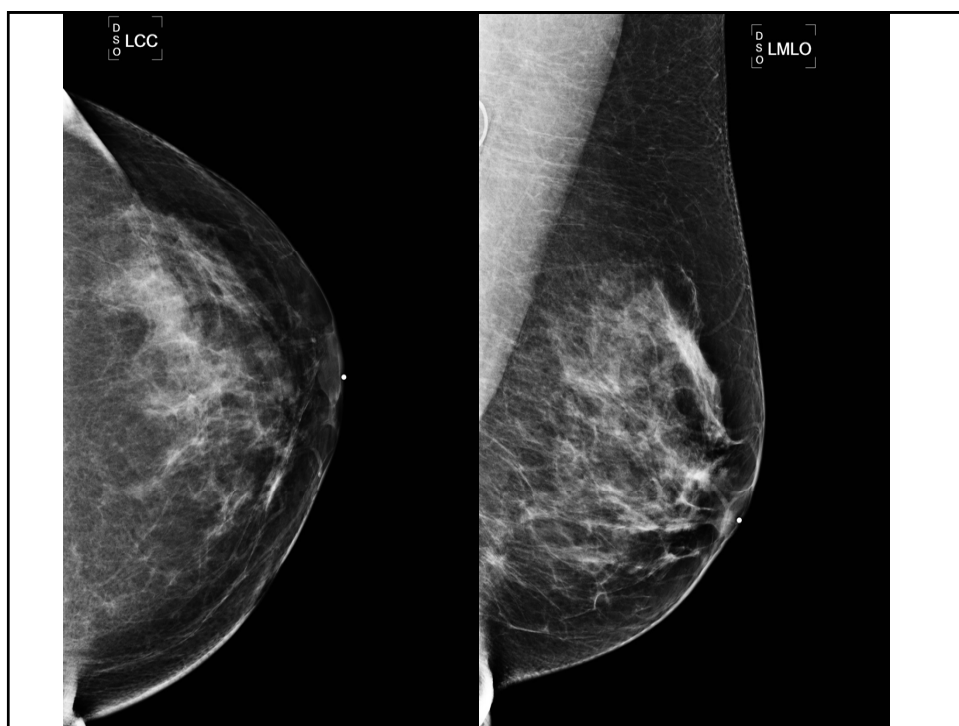
Digital Breast Tomosynthesis

Radiation Dose	mSV
Standard 2D FFDM	0.5
Standard 2D FFDM + 3D Tomosynthesis	1.0
Average Annual US Background Exposure	3.0
Average Annual Colorado Background Exposure	4.0
3D Tomosynthesis + Synthetic Composite 2D Views	0.5

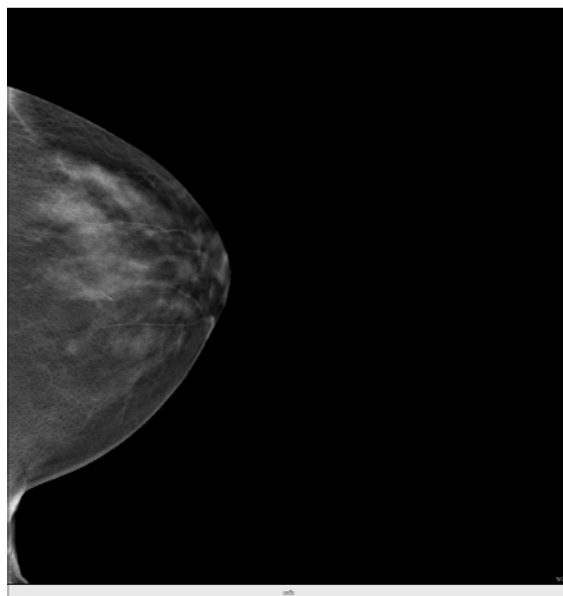


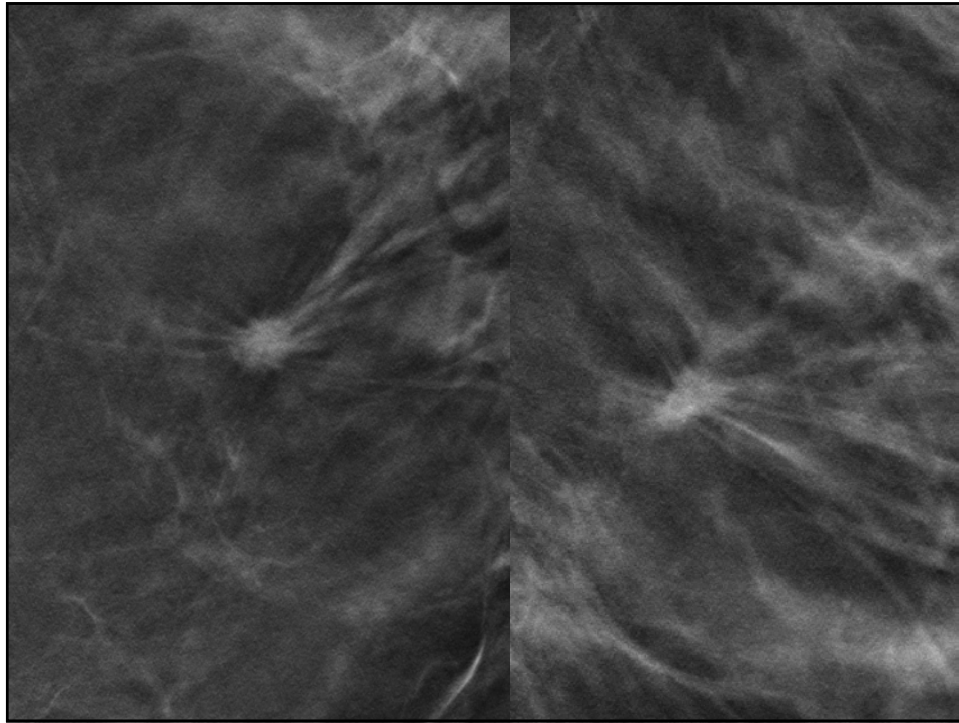
Case 1 video





Case 2 video



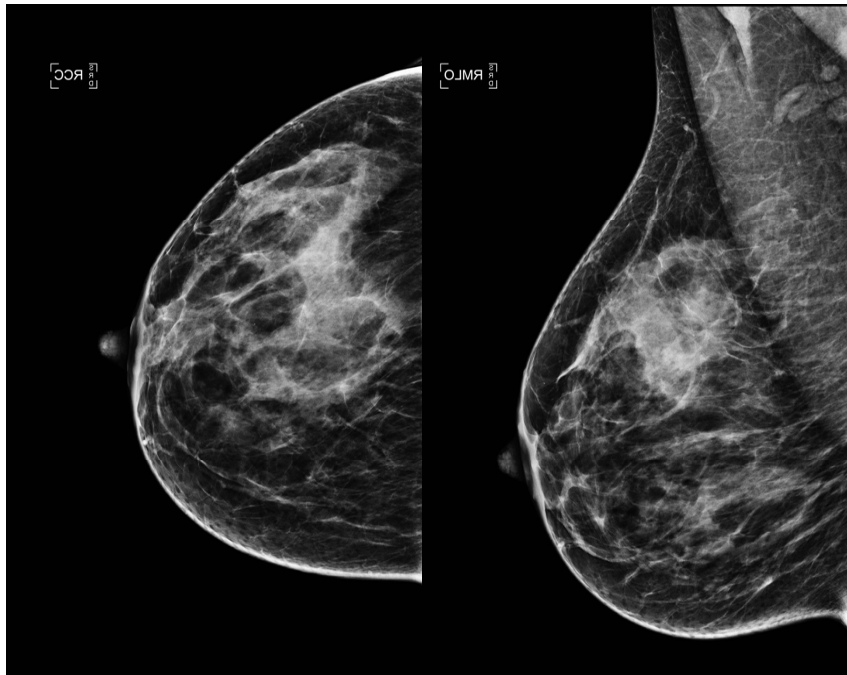


Breast MRI

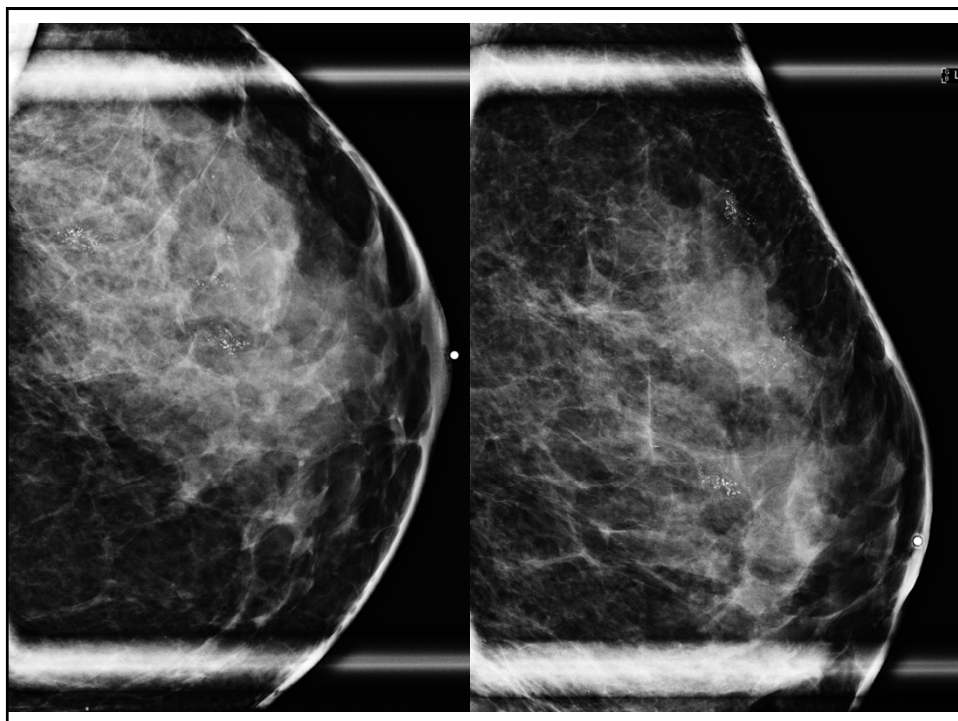
- **Non-controversial indications**
 - **High-risk screening**
 - **Monitoring response to chemotherapy**
 - **Axillary node malignancy suspicious for breast primary with negative routine imaging**
 - **Evaluation of equivocal imaging findings after complete imaging evaluation**
 - **No definite target for image guided biopsy**
 - **Evaluation of clinically suspicious nipple discharge with negative routine imaging**
 - **Evaluation of silicone breast implant integrity**

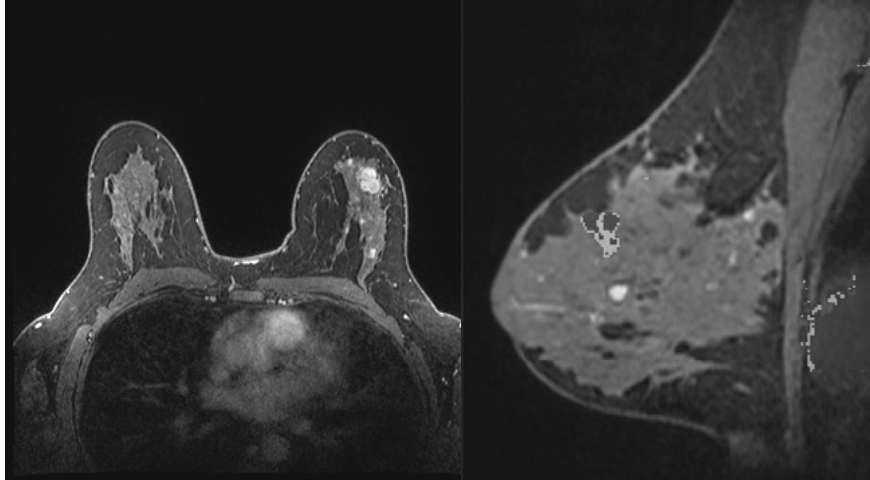
Breast MRI

- **When is breast MRI not indicated?**
 - Evaluation of imaging findings which can be targeted for biopsy
 - Evaluation of palpable findings with negative routine imaging



Breast MRI





Breast MRI

- **Controversial indications**
 - **Biopsy proven malignancy**
 - Evaluating extent of disease
 - Evaluating the contralateral breast
 - Cancer staging and contralateral screening
 - » More accurate than mammography and US in determining size/extent of cancer
 - » MRI will detect additional areas of cancer in 10-37%(16% average)
 - » Identifies occult contralateral cancers in approximately 4% of patients
 - No current evidence
 - » Improved mortality
 - » Improved prognosis
 - » Improved surgical management

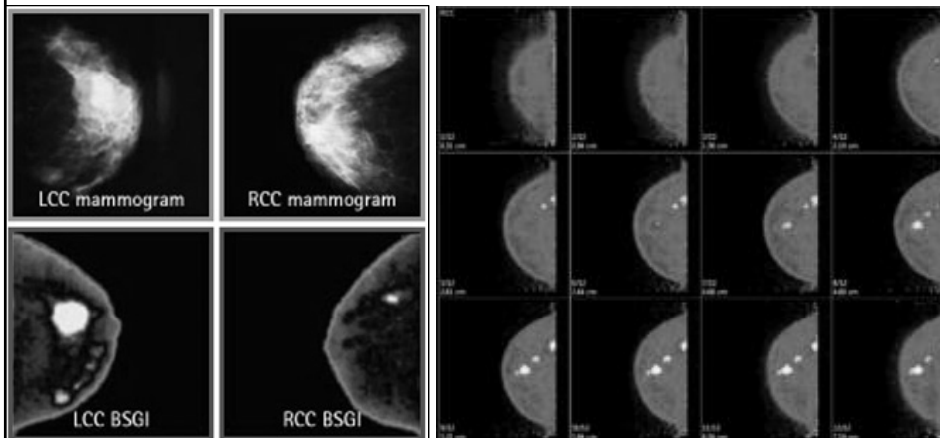
Molecular Breast Imaging

- **Breast Specific Gamma Imaging(BSGI)/Scintimammography**
 - Technetium 99m Sestamibi(Cardiolite)
 - Technetium 99m Tetrofosmin(Myoview)
- **Positron Emission Mammography**
 - F-18 Fluoro-deoxy-glucose

Molecular Breast Imaging



Molecular Breast Imaging



Molecular Breast Imaging

- **Proposed indications**
 - Radiodense breast tissue difficult to image
 - Evaluate suspected cancer recurrence
 - Evaluate extent of known cancer
 - Evaluate lesions for biopsy/treatment planning
 - Screening high risk patients
 - Evaluate palpable abnormalities not demonstrated on mammography or ultrasound
 - Additional evaluation when MRI unavailable or possible
 - <http://interactive.snm.org/docs/jnmt-1210b.pdf>

Molecular Breast Imaging

- **Advantages**
 - **Similar sensitivity and increased specificity relative to MRI**
 - **Similar positioning to mammography. Ease of interpretation.**
 - **Cost**
 - **Patient comfort**

Molecular Breast Imaging

- **Disadvantages**
 - **Ionizing radiation/radiation dose**
 - **Less supportive data**
 - **Not replacement for mammography**

	Mortality single exam age 40	Mortality single exam age 60	Mortality annual exams ages 40-80
Mammography	1.3	0.3	20
BSGI	33	27	
PEM	31	26	

- **Hendrick, Radiology 2010. “Radiation Doses and Cancer Risk from Breast Imaging Studies”**
LAR-Lifetime attributable risk (per 100,000 studies)

Contrast Enhanced Mammography

- **FDA approved device October 2011**
 - **Provides functional assessment of vascularity/neovascularity**
 - **Approved for use in patients when “Mammogram or ultrasound is inconclusive”**
 - **Dual-Energy Technique**
 - **20% increased radiation dose over standard mammography**
 - **Drawbacks**
 - **Require intravenous contrast**

Contrast Enhanced Mammography

